UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL MEETING

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TUESDAY

JUNE 20, 2000

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The panel met at 8:00 A.M. in Salons A, B, and C of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland 20877; Dr. Anne B. Curtis, Chairperson, presiding.

PRESENT:

DR. ANNE B. CURTIS, M.D., Chairperson
KENT R. BAILEY, Ph.D., Consultant
ROBERT DACEY, Consumer Representative
RENEE S. HARTZ, M.D., Member
GARY JARVIS, Industry Representative
WARREN K. LASKEY, M.D., Consultant
TONY W. SIMMONS, M.D., Member
CYNTHIA M. TRACY, M.D., Consultant
GEORGE W. VENTROVEC, M.D., Consultant
MEGAN MOYNAHAN, M.S., Executive Secretary

FDA REPRESENTATIVES:

MICHAEL BAZARAL, M.D.
JAMES E. DILLARD, III
BRIAN E. HARVEY, M.D., Ph.D.
MARK N. MELKERSON, M.S.
STUART PORTNOY, M.D.

SPONSOR REPRESENTATIVES:

JIM BULLOCK
PAUL FRIEDMAN, M.D.
GERHARD HINDRICKS, M.D.
ERIC KOEHLER

PUBLIC SPEAKERS:

HUGH CALKINS, M.D.
DALE DEVRIES, M.D.
JOHN FISHER, M.D.
MARSHALL STANTON, M.D.

C-O-N-T-E-N-T-S

OPEN PUBLIC HEARING

P-R-O-C-E-E-D-I-N-G-S

(10:12 a.m.)

CHAIRPERSON CURTIS: All right, I'd like to call this open meeting of the Circulatory System Devices Panel to order.

And the first order of business is Jim Dillard wanted to make a few remarks.

MR. DILLARD: Good morning. Thank you, Dr. Curtis.

There's a couple of things that we like to do on a regular basis when we get our advisory committee together; and one of them is to update you, as well as the public, about what's happening in the division, number one; and, number two, just to give you a brief update about your previous panel meetings and, and what we actually do with your recommendations.

So, what I'd like to do is just very briefly touch on those two; and then do one other, I think, good order of business that we don't get to do very often; but I think today is an appropriate time.

As most of you know, or, at least, this is

my second panel meeting; I think my first panel meeting was either the first or second week I was actually on the job, so I'm now here, and they haven't run me off yet, so -- .

My name's Jim Dillard, and I am -- I've been at the FDA for about 14 years; and I have been recently appointed the Director of this Division. And right now, a couple of things are happening within the Division of Cardiovascular and Respiratory Devices.

I have two acting Deputy Directors, Mark Melkerson and Brian Harvey, who are both long-time FDAers also, who I've known for quite a number of years, who are helping me out on an acting basis to take a look at the Division, as well as make some process changes, and kind of help the staff, I think, to look at a lot of the new FDAMA law that was passed, as well as take a look at how better to streamline the work within the Division.

To that end, this is the current structure that we have in the Division; and we are, right now, undergoing a reorganization or a potential reorganization, and we are in negotiation with our

union that represents our employees; and trying to come up with a good structure that will both alleviate, I think, some of the inefficiencies that are in, I think, normal government processing, as well as our particular division. But, I think, health -- help out our staff, predominantly, who have been quite overworked over the last two or three years.

The other good part is that we have been able to hire about four or five new employees that are scientific staff, as well as three new secretaries. So, we are in a phase, although it's, it's just closing now, of being able to backfill some of the positions that we've been in dire need of over the last two to three years.

And I think that will help, overall, not only in our interactions with you on the Advisory Committee, but with the industry that we regulate also.

This structure now, as you see, has five branches. It's four scientific branches and one support branch. And the structure we're going to be moving to, quite possibly, is going to be more of six

scientific branch areas; and we won't have a, a special branch that is for support of the entire division.

I, I can't really go into too much details, because some of that may change over the next two or three weeks, during some of the negotiation; but that's the current thought process that we'll be moving towards in the future.

So, hopefully, by the next Advisory Committee meeting, we'll be able to lay out for you exactly what the new structure is, and who the management is, and what we're actually going to be doing the next two or three years for the division.

Okay, Christy? You can go ahead and shut that off.

Real quickly, at the last Advisory Committee meeting, we brought three issues before you. We had rate responsive pacemakers, spinal cord stimulation for angina, and various devices for atrial fibrillation and asked you for predominantly clinical input, study design input, as well as a little bit of a reality check about some of the regulatory efforts

that we had been moving forward with.

And I think it's been both helpful to us, and to the industry, that we've sat down with since that panel meeting, as well as we'll continue to sit down, about some help, some good clinical help, some good statistical help, about what are important things for us to really think about.

And, and I wouldn't be surprised that, in the future, we continue those types of efforts, where we may be coming to you a little bit more informally, asking for your good clinical, as well as pre-clinical, opinions on various issues of clinical design that we might be struggling with at the time.

I think that being able to air some of those concerns, as well as having input from industry and the public, helps to put them in the forefront, so that when we sit down and we actually do a lot of the behind-the-scenes work that's not necessarily out in the open, we're able to have a little bit of a more level footing when we're dealing with the individual manufacturers. So, that's currently where those efforts are.

So, without further ado, I have two things that are happy things and sad things at the same time. And we have two panel members who have graciously served very diligently on this particular Advisory Committee for quite some number of years. And, being that I've only been here for about three months, I don't have -- yes, I do. I stand corrected, I do have the time that your terms actually were here; although I think that probably there's -- there's a lot more to that. You probably have participated a lot longer than even these plaques say.

Both of these individuals have spent countless number of hours not only in front of the public, but, I think, behind the scenes, too, looking at submissions, giving us input on informal types of contacts, as well as formal contacts; and I, I think we will sorely miss both of these two individuals.

But I have to say that the numbers of years that you've served, and the time that you've put in, is greatly appreciated on the side of the FDA, as well as the American public, and public health in general. Because I think without your particular help

and support, it's impossible to move forward with programs that really benefit all the individuals, including ourselves, that occasionally become patients, either in the earlier or later years of our, of our lives.

So, with that, I'd like to just read: Dr. Tony Simmons, Associate Professor of Cardiology, Wake Forest University. This is a letter from Dr. Haney, which reads:

Dear Dr. Simmons: I would like to express my deepest appreciation for your efforts and guidance during your term as a member of the Circulatory System Devices Panel of the Medical Devices Advisory Committee. The success of this Committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the participation and advice of the non-governmental health community.

In recognition of your distinguished service to the Food and Drug Administration, I am pleased to present you with the enclosed certificate. And it's signed, Dr. Jane Haney.

And if I could speak with any higher tone, I might even sound like Jane Haney.

(Laughter)

And we'll give you both a big round of applause as soon as this is over.

And, Dr. Simmons, I believe your term was from 1997 to the year 2000, I think is what your plaque had on it. So, for your three plus years of service, I, I thank you personally.

And the other is to our distinguished Chair, Dr. Curtis.

Dr. Curtis, Professor of Medicine, Department of Medicine, Division of Cardiology, University of Florida.

And I will -- I would like to read yours, although it may sound like something similar.

I would like to express my deepest appreciation for your efforts and guidance during your term as a member and Chair of the Circulatory System Devices Panel of the Medical Devices Advisory Committee. The success of this Committee's work reinforces our conviction that responsible regulation

of consumer products depends greatly on the participation and advice of the non-governmental health community.

In recognition of your distinguished service to the Food and Drug Administration, I am pleased to present you with the enclosed certificate.

Jane Haney, Commissioner of Food and Drugs.

And Dr. Curtis's plaque reads her term from July 7th, 1996, to June 30th, 2000.

So, for your four years of participation, I also would like to thank you.

(Applause)

In closing, just one more time, a thanks, and you will be missed; but the great thing about advisory committees is that we never take you off our consultant list, so you never know when we might call you back. Thank you.

CHAIRPERSON CURTIS: Thanks.

Okay, now to more mundane matters. We have to read the conflict of interest statement.

MS. MOYNAHAN: Thanks.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests.

However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the government.

Therefore, waivers have been granted for Doctors Anne Curtis, Renee Hartz, and George Vetrovec for their interests in firms that could potentially be affected by the panel's recommendations.

Copies of these waivers may be obtained from the agency's Freedom of Information Office,

Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency also took into consideration other matters regarding Doctors Curtis, Vetrovec, Cynthia Tracy and Warren Lasky. Each of these panelists reported interest in firms at issue, but in matters that are unrelated to today's agenda.

The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRPERSON CURTIS: Okay, the next thing I'd like to do is have all the panel members introduce

themselves.

As -- I'm Anne Curtis, the cardiac electrophysiologist from the University of Florida.

DR. SIMMONS: Tony Simmons, Wake Forest University.

DR. CRITTENDEN: Michael Crittenden, cardiac surgeon, West Roxbury, VA.

DR. LASKEY: Warren Laskey, interventional cardiologist, University of Maryland.

DR. BAILEY: Kent Bailey, biostatistics, Mayo Clinic.

MR. DACEY: Robert Dacey, Consumer Representative, Longmont, Colorado.

MR. DILLARD: Jim Dillard, Director, Division of Cardiovascular Respiratory Devices, FDA.

MR. JARVIS: Gary Jarvis, Industry Representative to the Panel.

DR. TRACY: Cynthia Tracy; I'm an electrophysiologist at Georgetown here in town.

DR. VETROVEC: I'm George Vetrovec at the Medical College of Virginia, Virginia Commonwealth University in Richmond. I'm an invasive cardiologist.

DR. HARTZ: Renee Hartz, cardiac surgeon, Tulane University.

MS. MOYNAHAN: Megan Moynahan, Panel Executive Secretary for the Circulatory System Devices Panel.

CHAIRPERSON CURTIS: And I just want to also state that the transcriptionists are asking that each one of us identifies him or herself each time we speak, because they're having a little trouble keeping up with who's speaking at each time. So, even though it sounds repetitive, it'll help them out.

The subject of this meeting this morning is general indications for implantable cardioverter defibrillators. And we are going to start with a short FDA presentation, followed by the open public hearing.

So, FDA?

DR. BAZARAL: Good morning. My name is Michael Bazaral, I'm a medical officer, working in the Office of Device Evaluation.

The FDA is considering a revision of the implanted cardioverter defibrillator guidance, which

we'll be undertaking, using the Good Guidance Practices Policies.

Relative to that guidance, at this meeting, we're asking the panel to discuss advantages and disadvantages of a proposed intended use statement.

A proposed intended use statement is that the implantable defibrillator is intended to provide possibly ventricular antitachycardia pacing and ventricular fibrillation, certainly, for automated treatment of life-threatening ventricular arrhythmias.

And this is, you'll note, a functional intended use statement; and the statement does not specify which patients are at risk of life-threatening ventricular arrhythmias.

The intended use statement now, or at least the basic intended use statement now used for ICDs, is that the implantable defibrillator is indicated for use in patients who are at high risk of sudden cardiac death due to ventricular arrhythmias and who have experienced one of the following situations:

And we could have the next slide. I put these up here for reference.

The, the conditions are either a survival of at least one episode of cardiac arrest, manifested by loss of consciousness due to ventricular tachyarrhythmia; or recurrent, poorly tolerated, sustained ventricular tachycardia.

These indications are, in essence, the entry criteria for the studies that were used to demonstrate effectiveness and safety of the ICTs; and indications were presumably chosen to assure a high prevalence of life-threatening ventricular arrhythmias in the studies of the devices.

The indications, as stated, give the impression that the FDA-approved labeling for these devices defines the population at risk. That was not the purpose of the studies, at least for the greater part. The purpose of the study were to evaluate the safety and effectiveness of the devices in a high prevalent population.

There is an exception. One manufacturer's guidance of current intended use does include an

additional patient population. These are prior myocardial infarction, a left ventricular fraction of 35 percent or less, a documented episode of nonsustained VT with an inducible tachyarrhythmia, and some other comments.

Indications based on the MADIT trial that showed improved survival for this population treated with this brand of defibrillator.

The proposed functional intended use statement that is for automated treatment of life-threatening ventricular arrhythmias is of recognition that although the data submitted to the FDA for ICDs are from trials designed to evaluate safety and effectiveness of the ICD in a population known to be at risk, the single manufacturer ICD trial that was submitted to the FDA generally do not address the question of which patients are at risk of ventricular tachyarrhythmias.

The proposed intended use statement does rely on implicit assumptions. One assumption actually demonstrated most of the times that the approved ICDs can treat ventricular arrhythmias; and this is

demonstrated for each of the currently approved devices.

We're also assuming that the detection defibrillation by an ICD will not be affected by the differences among cardiomyopathies. Much of the ICD data is derived from patients who have ischemic cardiomyopathies. We assume that ventricular fibrillation, for example in patients with inherited arrhythmogenic cardiomyopathies would also be treated by ICDs. And published studies, though limited, generally support this assumption.

We also assume that the differences among patients are minimized by individualized settings. The settings are determined by testing, both at implantation and at follow up in, in current practice.

And, finally, we're assuming that the information on diseases or conditions that cause life-threatening ventricular arrhythmias is available to the physician from sources other than the device labeling. Examples of this are the American Heart Association, American College of Cardiology and Guidance publications, as well as reports of

individual studies.

In the past, functional intended use statements have been, have been applied by the FDA to other devices. One prominent example is the artificial heart valves that are generally indicated for replacement of malfunctioning native or prosthetic heart valves.

And the cardioballoon angioplastic catheters are also an, an example. And these are indicated now for balloon dilatation of the stenotic portion of a coronary artery or graft for the purpose of improving myocardial profusion.

And this approach, that goes to say, a approach that doesn't specifically identify the, the population, is similar to what we're proposing here.

For implementation, the functional intended use statement would be incorporated into an ICD guidance for new ICDs. The guidance for a new ICD would state the clinic trials information would appear in the, in the label in the summary of clinical data. But only when the clinical data result from the study of one manufacturer's device, the one that's being

labeled.

And implementation might also include that the functional intended use statement would be available as an optional alternative for currently approved ICDs. We currently know that these ICDs can defibrillate patients.

And finally, that other device functions incorporated into the ICD or unique ICD functions, would have to have separate or additional intended use statements, other than the one that we're asking on -- for comments on today.

If you can have the last slide, then.

So, in summary, the FDA is asking the panel to discuss the, the advantages or disadvantage of a proposed intended use statement, that's a functional intended use statement, that does not specify which patients are at risk of life-threatening ventricular arrhythmias.

And, Christy, I suspect you can leave that up there for reference when the panel's discussing that.

Thank you.

CHAIRPERSON CURTIS: Okay, we'll move on now to the open public hearing.

There are several people who have requested time to speak today. We'll start with Dr. Hugh Calkins from Johns Hopkins University, representing NASPE.

And, as you step to the microphone, if you would state what your financial interests are in the, the sorts of products that are being discussed.

DR. CALKINS: I'm Hugh Calkins from Johns Hopkins, and I represent NASPE.

No financial conflicts to discuss today.

Can you have the first slide, please?

Good, next slide?

This introduction, NASPE, the North American Society of Pacing and Electrophysiology is a professional organization of about 3500 physicians, scientists, and other health professionals, expert in the study and management of patients with cardiac rhythm disorders.

The mission of NASPE is to improve the care of patients by promoting research, education, and

training, and providing leadership towards optimal health care policies and standards.

Next slide.

Each year in the United States, approximately 200,000 patients undergo placement of a permanent pacemaker; and approximately 50,000 patients undergo placement of an implantable defibrillator. And over 50,000 patients have an electrophysiology study or, or catheter ablation procedure performed. And most of these procedures are performed by members of the NASPE organization.

Next slide.

I'm, I'm here on behalf of NASPE to say that NASPE supports the FDA proposed revision to the label indications for ICD use, which are under consideration by the panel today. And you've heard that before, and I will not repeat it.

Could you go to the next slide.

And, again, we again have heard what the current label indications for defibrillators are. I think it's important to note that these indications are really out of date as far as clinical practice.

For example, an indication today is that patients have to have recurrent, poorly tolerated, sustained ventricular tachycardia.

And as we'll slee -- see in a few slides, the, the efficacy in improv--in improving survival has been shown for patients who have had only one episode of sustained ventricular tachycardia or none at all.

Next slide.

And this, again, goes over the other current label indications for implantable defibrillators in the population of patients with an ischemic cardiomyopathy, inducible VT that were studied in the MADIT population.

Next slide.

Though NASPE agrees with the FDA rationale for proposing the change in label indications for use, and that is that current indications for use of implantable defibrillators are not consistent with current clinical practice, which is based on clinical information, which is widely available, and which forms the basis for current practice, as well as current guidelines for ICD and pacemaker use.

NASPE feels it'd be more accurate if the ICD indications is that the device -- the device's known function, functionality and does not attempt to define the population at risk. And, again, as we've heard earlier, there's precedent for this in the case of balloon angioplasty devices and heart valves.

Next slide.

Let me just go over two studies that I think pertain to our, our, our consideration today.

The first is the AVID study, which was a study which was designed to determine the relative efficacy of the ICD, first as anti-arrhythmic therapy in patients with aborted sudden cardiac death or hemodynamically unstable VT.

And this study involved a little over 1,000 patients. And, again, to get into the study, patients have to have had an episode of aborted, aborted sudden cardiac death, sustained VT with syncope, or hemodynamically unstable VT, with an ejection fraction less than 40 percent. And, again, there only had to be one episode of, of hemodynamically unstable VT to get into this trial.

And the patient population, the mean age was 65 years; ejection fraction, 31 percent; 81 percent had ischemic heart disease; and 45 percent had had a prior episode of sudden cardiac death.

Next slide.

This is -- shows the survival of patients in this trial, with the red line showing the patients treated with an implantable defibrillator; and the white line showing patients who were randomized to EP guided and to arrhythmic therapy. And there was a 39 percent reduction of mortality of one year; a 31 percent reduction of mortality at three years.

Next slide.

What is interesting and pertains to our discussion today is the results of the AVID Registry, which were patients that met inclusion criterion for the study, but either did not want to be entered or, or actually -- they were considered, screened for the study, but they did not fit enrollment criterion.

And in this publication, published in circulation late last year, they looked at the survival of a little over 4,000 patients entered in

the Registry, enrolled before 1997, and they looked at the national health index to find out if they were alive or dead.

And shown below is the mortality rates at 17 months of follow up. So here is the entry criterion or, or the presenting arrhythmia; and this is the mortality at about a year and a half. And as we know, that, that the ICD is indicated for patients who have had an episode of sudden cardiac death that had a 17 percent mortality at, at one and a half years.

But even patients with stable VT had a very similar mortality; or patients who presented with syncope and had an impaired ventricular function had a fairly high mortality.

So the conclusion of this paper was that patients seemingly at lower risk of ventricular arrhythmias have a high mortality, similar to that of higher risk AVID-eligible patients.

Next slide.

There's other examples where the current guidelines for defibrillator implantation don't really

apply; and our current clinical knowledge is evolving at a much faster rate.

This is a small study, but there have been others like it by Fred Morady and colleagues in the University of Michigan, where they looked at patients, 14 patients, who had presented with syncope, had a non-ischemic cardiomyopathy, a normal EP study; and we know in that setting that EP testing has limited sensitivity, and they, they put an implantable defibrillator in these patients.

And then they also looked, as a comparative group, at 19 patients who presented with a cardiac arrest, also had a non-ischemic cardiomyopathy, and also were treated with a defibrillator.

And what they found is, during two years of follow up, seven of the 14 patients with an ischemic dilated cardiomyopathy and syncope, with no inducible VT, had an appropriate ICD shock due to VT or VF. And this, in fact, was a higher percent, as compared to the patients who initially presented with cardiac arrest.

So these types of data, and there's others like it from many centers around the country and around the world, support ICD implantation in patients with an idiopathic dilated cardiomyopathy, unexplained syncope, a negative EP study, and impaired ventricular function.

And these are example where the current practice has evolved much quicker than the, than the FDA guidelines, as they currently exist.

Next slide.

There's other examples in terms of the long-QT syndrome. This is a paper also published in circulation last year. And, again, this gives you a feel for how new data affects clinical practice. Thirty-seven patients with long-QT syndrome treated with pacing and beta-blocker therapy after failure of beta-blocker therapy alone, and they followed these patients for six, a little over six years.

And they found that, over 6.3 years of follow up, there was a 24 percent incidence of sudden cardiac death or aborted sudden cardiac death. And their conclusion was that combination therapy in

long-QT syndrome patients results in an unacceptably high risk of potential fatal arrhythmias during follow up.

And, again, this is an example where defibrillators are now being placed in this type of patient subgroup.

Next slide.

The rationale for NASPE's support of the proposal under consideration today is that it recognizes that the decision to implant a defibrillator is a medical decision made by patients and their physicians.

A decision to recommend ICD placement is based on the most current clinical evidence, which continues to evolve as more information becomes available.

The ACC/AHA and NASPE publish guidelines on the indications for ICD and permanent pacemaker implantation which are updated on a regular basis and serve as a, as a cornerstone for, for the evolving guidelines. And these guidelines also, I think, prevent overuse by the medical community.

And that will end my discussion. Thank you again.

CHAIRPERSON CURTIS: Thank you.

Dr. Fisher?

DR. FISHER: Thank you.

I'm John Fisher; I am a Professor of Medicine at Albert Einstein College of Medicine.

And I am here today, supported by Medtronic for my expenses for the vaca--for the trip and for the time away from practice. And I'm also a consultant for Medtronic.

I've been involved with the defibrillator; our institution, which I've been associated with during that full time, was the second place, along with Stanford, to be approved for the defibrillator, back in the eighties, after, after Hopkins. So, it's been interesting for me to watch the, the evolution of what's going on with indications over the years.

Next, please.

Much of what I'm going to say is remarkably similar to what Dr. Calkins has said; and in turn, toward what Mr. Dillard had said. So this is

going to be something which I can move over fairly quickly.

The current FDA label indications have been reviewed and are -- have a tendency to be diagnosis-oriented; and, for clinicians, this can sometimes be a problem, because we have indications from the FDA, in terms of such items as the particular exception for the Guidant device; we have indications from the other organizations, such as PEARS, the Health Care Finance Administration, and so forth; and there are indications from ACC/AHA, and NASPE guidelines; and these are not all entirely in concord with each other. And they don't move along at the same pace.

Next, please.

Again, we've talked about the FDA label indications and the exception.

Next.

The proposed label indications from the FDA panel pack that Mr. Bazaral presented, which I think is very important.

The functional indication that the ICD is

intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automatic, automated treatment of life-threatening ventricular arrhythmias is a very important step, I believe. And particularly the fact that there is no statement of which specific patients are at risk for life-threatening ventricular arrhythmias.

Next.

The FDA rationale, as we understand it, for the proposed change in label indications are that current indications are -- for use are not consistent with current practice. And the label indications do not incorporate some of the clinical information which is widely available and forms the basis of clinical practice; and Dr. Calkins presented some of these.

A more accurate label, the label would be more accurate, if the stated indication is for the device's known functionality, what can it do; can it stop V tach; can it stop ventricular fibrillation; can it recognize them in the first place? And does not attempt to define the patient population at risk by -- on the basis of specific diseases.

And, as mentioned before, there is precedent for this general functional indication; for example, in balloon angioplasty.

Next.

There are a lot of advantages to this change, proposed change, from a clinician's perspective. The decision to implant an ICD is a medical decision, made by patients and their physicians, based on the most current clinical evidence, and what is most appropriate for the individual patient.

And the FDA role is usually focused on established the safety and effectiveness of the ICDs; and the point has just been made by the previous speakers that the ICDs seem to work pretty well at both recognizing and defibrillating or treating arrhythmias, no matter whether they are from one kind of cardiomyopathy, or from another, or from a patient, perhaps, with no overt structural heart disease.

And current public and private payer coverage is broader than the current label indications.

Next, please.

Again, from the clinical perspective, other advantages are that manufacturers will be able to assist in the timely dissemination of clinical evidence relating to the use of ICD therapy.

For example, patient populations identified in Section IV of the panel pack, those with hypertrophic cardiomyopathy, long-QT syndrome, the MUSTT protocol recently published; and for future at-risk patient populations as new clinical trials are completed.

At the present time, for example, since the ICD is not specifically labeled for MUSTT-type patients or for long-QT syndrome, in patients who may, indeed, be at high risk, but have not had events, these labels are not included.

They would be included, however, in a functional labeling, as has been proposed. And, therefore, we support this proposed change.

Next, please.

There are some potential disadvantages from a clinician's perspective. We're always worried

about potential overuse of ICDs. We don't want everybody implanting ICDs willy-nilly in people who don't need them; they're expensive, they cost somebody some money; and the medical community does have overuse safeguards, however.

Most physicians do seek out the latest clinical evidence. And the clinical evidence, as I mentioned, for example from the MUSTT trial, just came out in December; it has not yet had time to be incorporated in the various labels.

The ACC/AHA and NASPE periodically produce guidelines on the use of these devices; and these are looked at very carefully by physicians when they make their decisions; and are helpful to physicians as we discuss the matter of paying for these with the various payers.

And the proposed label change does not affect coverage and reimbursement policies of the payers, who, in fact, themselves rely on the same evidence. They go look at these articles, whether they have to do with MUSTT or other things that are current, and they decide whether there is enough

clinical evidence, outcomes evidence, to justify payment for the implantation of the device.

Next, please.

So with that, I, I end the clinician's perspective on the proposed changes; and from a clinician's perspective, a clinician associated with Medtronic, I would like to voice my support.

CHAIRPERSON CURTIS: Dr. Stanton?

DR. STANTON: Thank you.

I'm Marshall Stanton; I'm a cardiac electrophysiologist; and I'm Medical Director and Vice-President of Therapy Development for Cardiac Rhythm Management Division at Medtronic.

Medtronic's position is that we agree with the proposed functional ICD labeling as described in the Panel Pack; and that it should be adopted.

And reasons for this from an industry perspective is that the proposal, proposed language is consistent with indications for use across manufacturers' PMA-approved ICDs.

We believe that this would promote industry cooperation in supporting clinical trials

that otherwise may not have occurred.

And, very importantly, education. It allows rapid dissemination of clinical trial results without the need for FDA approval. For example, PMA supplement should not be necessary for this.

Additional advantages: This reduces the regulatory burden, both for FDA and for industry. It's consistent with the least burdensome provisions of the FDA Modernization Act of 1997.

New studies of at-risk patients would not require an IDE application; and this would encourage further clinical research.

There'd be no need for PMA supplements prior to the dissemination of clinical trial results for every specific at-risk patient population studied. For example, in the panel pack, the FDA identified four patient populations that there's reasonable support for use of the ICD in now, beyond the labeled indications.

And if each of the five ICD manufacturers presented data, that would be 20 PMA supplements that FDA would have to review. And this would also be true

for additional patient groups that are currently under study; for example, in the MADIT II trial, SCD-HeFT, and definite ICD trials.

This also would allow the FDA to focus on new product approvals, rather than on the above.

It's important to also acknowledge any potential disadvantages; and the argument could be made that it could discourage clinical research on specific high patient populations where trials have not yet been completed. But the manufacturers are committed to supporting clinical research for a number of reasons.

Firstly, physicians use clinical decision making based on clinical evidence. Payer's technology assessment requirements -- those of you who are familiar with the MCAT process going in HCFA, as well as the technology assessments of private payers -- know that evidence must be provided before coverage will occur.

And, also, there's evidence from on-going clinical trials, such as SCD-HeFT, IRIS, HCM, and long-QT syndrome trials as well.

Physicians themselves are highly committed to continued research to identify appropriate patients that are most likely to benefit from ICD therapy. In fact, companies receiving funding requests on a regular basis. Physician-sponsored research is wide spread. Manufacturers sponsor much research today that is not intended for regulatory submission.

The quality of the evidence supporting clinical indications is taken into consideration in developing guidelines and in determining coverage and reimbursement.

So, in summary, Medtronics strongly supports the proposed change to a functional indication for ICDs. It is consistent with current clinical practice and the knowledge base. It enhances timely dissemination of clinical trial data; and it decreases regulatory burden.

I'd like to thank FDA for providing this forum for today's discussion and for their pro-active approach to ICD indications. Thank you.

CHAIRPERSON CURTIS: I, I believe Guidant also requested time? Mr. DeVries?

DR. DEVRIES: I think there's been a lot of discussion today about the, the indications. And instead of being redundant with another presentation that presents much of the same, we will be presenting a Guidant position.

I think everybody in this room realizes that Guidant, formerly CPI, was involved in pioneering this technology; and also pioneered a lot of key clinical studies that were related to identifying additional patient populations.

I may disagree with the FDA on why we conducted these trials; but, clearly, we were looking at patients who were at high risk. And having been involved in this for, for a lot of years, we do have a conclusion and a statement we'd like to make, so you want to put it up?

CHAIRPERSON CURTIS: Could I just say, I don't think you identified --

DR. DEVRIES: Oh, excuse me.

CHAIRPERSON CURTIS: -- yourself fully for the --

DR. DEVRIES: Yes, I'm --

CHAIRPERSON CURTIS: -- transcriptionists?

DR. DEVRIES: Sure. I'm Dale DeVries; I'm Vice-President of Product Assurance and Regulatory Affairs and Clinic Studies at Guidant.

I'm an employee of Guidant and I own stock in Guidant.

As you can see without going through the entire statement, we're also in support of the change in the indication that has been proposed by the FDA, NASPE, and others prior to this.

I would like to just make a couple other comments. It's been suggested to us that maybe Guidant has the most to lose by the change in this indication, and we really don't see it that way. We think that the patients have the most to gain by a change in indications. We believe that the new indications provide the physicians with the flexibility to, indeed, treat those patients who are at high risk. So we don't see it that way.

I'd like to also echo what Dr. Stanton said. We don't see this as a situation where industry may be less inclined to do clinical trials to bring

forward more information related to patients who are at high risk. In fact, it might, indeed, facilitate doing more clinical trials, where we can collect more information related to different patient subgroups; so we would agree with Medtronics' conclusion related to conducting clinical trials. We, as a company, would not reduce the amount of clinical trials we're doing because the indication was expanded in this method.

So we'd like to also thank the FDA for this opportunity. We also believe that it's the correct direction for the FDA to take this particular therapy on this particular device. And it is a general device indication; but the device was designed to treat these kinds of arrhythmias.

So we, we strongly agree and recommend agreement on this proposal.

CHAIRPERSON CURTIS: Thank you.

Any other members of the public who would like to get up and make a statement?

(No response)

CHAIRPERSON CURTIS: If not, then we'll close the public hearing.

And the only other order of business it seems we have is to discuss the, the one question to the panel, which is the advantages and disadvantages of the proposed general indication for use statement. And we've seen it up there several times; I don't think we need to repeat that.

Anybody want to open it up?

DR. TRACY: What they said.

(Laughter)

CHAIRPERSON CURTIS: I mean, we have NASPE, two of the major manufactures, and the FDA all agreeing on this; I don't think this is going to be too hard.

DR. SIMMONS: I, I just don't have much to add, either; I mean, I think it's great -- it's a great idea.

CHAIRPERSON CURTIS: I, I think it's a great idea. I think -- I think it makes a lot of sense.

The, the upsides were discussed; I think there's very little downside to it. It's going to simplify things; and I applaud the FDA for thinking of

this and putting it forward. I think it's going to simplify future trials of new defibrillator therapy.

DR. BAILEY: Can I just ask one thing?

CHAIRPERSON CURTIS: Uh-huh.

DR. BAILEY: A naive question. Can the functionality of these devices depend on the patient population? Is that an issue that would need to be considered?

CHAIRPERSON CURTIS: I'm not sure what you're asking, exactly.

DR. BAILEY: Is the functionality of the devi--of these devices independent of the patient population? Is that an issue that may --

CHAIRPERSON CURTIS: Basically, yes. --

DR. BAILEY: -- could come up in the future?

CHAIRPERSON CURTIS: -- I mean, you know, a defibrillator can treat ventricular tachycardia and ventricular fibrillation. And, and that's what the general indication is for, and they all do that.

And, currently, today, they, they basically will have pacing capabilities as well. And

they were doing single-chamber devices.

And so, a lot of what comes out now, in terms of when you get a new defibrillator, it's more bells and whistles. The manufacturers are adding treatments for SVT, as well as for VT, that, that sort of thing. But in terms of its basic functionality, it's always the same.

And the patient populations that are being studied; I mean, they're all -- basically, what it comes down to is different patient populations that possibly hadn't been thought of before. One example was the syncope with non-ischemic cardiomyopathy. That's not a currently labeled indication, but there's more and more evidence that that may be appropriate.

And so, you know, the device is be -- is being used to treat the same thing; it's just that we're identifying potentially new patient populations that could benefit from the device.

And so, here, what we're talking about is not having to say specifically that it's been proven effective in this patient population in terms of a labeling indication, that there are other ways of

doing that.

We, we still do clinical trials, because if you want to -- the payers to pay for it, and the guidelines that ACC and NASPE publishes to reflect these new indications, then you have to have trial data to support that.

But it also wouldn't require the regulatory process to change the labeling each time.

MR. DILLARD: Jim Dillard. Let -- let -- I'd like to make one comment --

CHAIRPERSON CURTIS: Okay.

MR. DILLARD: --because there are a couple things that came up, and I, and I just want to clarify that particular point, because there are some, some real particular things to consider here that I think are worthwhile putting on the table.

And one being, I believe that Dr. Stanton put up on one of his slides, the potential advantages being no need for a PMA supplement prior to dissemination of clinical trial results for every specific, at-risk patient population studied.

And while I would, in general, agree with

that particular statement, there's another implication that potentially goes on with that; and I think that's the point you're getting at, Dr. Curtis, which is would a manufacturer need to submit a PMA supplement if they wanted to specifically state in their promotional and advertising material that this product could be effective in a specific patient population?

And there is a little bit of a distinction in terms of the way we regulate the products and the labeling that I think is worth drawing here.

And that being, if the manufacturer was going to disseminate available information or available data as likely supporting information about how the product may be used in the clinician's hand, then I would agree that that could happen without a PMA supplement.

But if either one of those manufacturers, and other manufacturers, want to, to specifically make a case in their labeling that their product was effective in the treatment of a specific patient population, I think that would be something that we would probably have some discussion with the sponsor

about; whether or not there would need to be a prior submission of a PMA supplement; whether or not there would be another potential mechanism.

But I think because of the fact that it is still a PMA-approved product, that we would need some sort of interaction with the sponsor prior to them going out with definitive statements about their device being effective in a new patient population.

And only one other small distinction, which is, I think it would be easier for those particular indications where there's already data that exists in the literature, where that case may be able to be very broadly made at this point, versus other new indications -- like congestive heart failure, for example -- where we're very interactive with the sponsor and they want to make a pro-active statement in their labeling about the product being effective or not effective. Hopefully, that they're not effective; but that they are effective in a particular patient population.

And in those cases where it would be a new indication for use, I still think there would be prior

FDA involvement to them being able to add it to their labeling.

CHAIRPERSON CURTIS: I, I, I can understand if -- that you want to have something in the labeling, saying that something -- it's safe and effective for X new indication, that they'd have to have the PMA supplement.

But, so, if, you know, let's say you had some clinical trial data that showed that -- oh, I don't know -- in, in, in patient -- in, in all patients with congestive heart failure, the device prolonged survival.

Are you saying, then, that in order to go out and put that in the -- in promotional literature, they'd have to change their labeling to do that? I mean, which would require a PMA supplement?

MR. DILLARD: Well, it, it -- this gets into a real gray area, so I was even, you know, worried about bringing it up.

But, but there's obviously -- we regulate any labeling that the company would put forward. So whether it's promotional material, it's technically

considered labeling.

And so, there's some gray area about whether or not the information actually is being disseminated as useful information for the clinician, which is one area; versus the information is actually being added to promotional material labeling, instructions for use manual, to actually say something about the data and whether or not, then, the product can be effectively used in that patient population.

So, there are different levels of labeling changes, which could require a different level of regulatory submission.

And I would just say the gamut kind of goes from real statements that are supported by data that may be available, so they're promoting that use in their labeling and promotional material. That would be something I think we would need to work with them in terms of some sort of information that we would look at prior to them being able to do that for a new patient population.

Versus dissemination of newer information that may be available for clinicians in terms of new

uses of the product; but the sponsor not specifically putting it in their promotional and advertising material. And, and that could be done, generally, without a prior pre-market approval supplement.

CHAIRPERSON CURTIS: So you're saying if a major clinical trial gets published in a major cardiology journal, they could take reprints of it and distribute --

MR. DILLARD: Distribute the information.

CHAIRPERSON CURTIS: -- it, but that's not considered --

MR. DILLARD: Right.

CHAIRPERSON CURTIS: -- promotional literature, per se.

MR. DILLARD: It, it's generally available literature. And I --

CHAIRPERSON CURTIS: Yes.

MR. DILLARD: -- think there's some gray area.

CHAIRPERSON CURTIS: Okay.

MR. DILLARD: I think if it's generally accepted by the medical community, that that is the

current state of the art. I don't think FDA would pro-actively go after manufacturers and say, "You know, you have to stop disseminating that information."

I, I think if it's something specific for the manufacturer, though, and it may be data that is for their particular product only, that is something that I would encourage the manufacturer to come in and at least discuss with us and try to work out a plan of whether or not we need a pre-market approval supplement, could we do it through an annual report, could we do it through a 30-day supplement; we have a lot of mechanisms, potentially, to handle this, where it does not have to be any long-term delay before it could actually be added. And I think we've got those mechanisms.

So, so, really, in just a -- so, just in summary, my point is that it may not be, and I didn't want people to get the impression, that it should be broadly interpreted. That if this particular proposal does go few -- go through, that there will never be a need for a PMA supplement prior to any labeling

changes.

And I just wanted to make sure that it's not quite that broad and everybody understood that.

CHAIRPERSON CURTIS: Okay.

DR. TRACY: Can, can I just ask a --

CHAIRPERSON CURTIS: Sure.

DR. TRACY: -- clarification, just a small clarification on that?

If one company, in the future, supports a, a study, multi-center study; and the device is found to be beneficial in that particular patient population, then the published literature can be used by another company to support the use of the device?

Is that -- or would they have to do something in order to use that information for their own product?

MR. DILLARD: Jim Dillard.

I'll make a general comment to that, which is once information becomes publicly available, any manufacturer can potentially utilize it for a pre-market submission.

So, to the extent that, I think, some of

the discussion today has been generalizable in a functional kind of way, across all the different device types, and not being specific to a particular disease state of patient population, to the extent that that literature could be generalized across other particular products, I think would be really the bearing behind how appropriate it would be to be utilized in somebody else's pre-market submission.

But, in general, commercially or publicly available information can be used by another manufacturer.

DR. VETROVEC: I, I have to ask the question, who's against this? Is there something I'm missing?

CHAIRPERSON CURTIS: No.

(Laughter)

CHAIRPERSON CURTIS: I think, I think -- and I think the comments from Guidant that some people might have supposed they could be against it to some extent was answered by them, that they support it, too.

So, no, actually, we're all on the same,

same side of this. So, you know, it seem -- it does seem very straightforward.

You know, and, and, and you've clarified some of the issues about the PMA supplement, and, and where this might not fit in; but, in most cases, this is going to change the way things are handled and make it simpler all the way around; so I, I don't think there's any problem here.

And this is not the sort of thing we're voting on, so I think we've got a very strong consensus. I haven't heard anybody say that they were against this change.

So, I think we can just go ahead and say we strongly support the, the FDA making this change.

And that's all we needed to cover about this, because there was just the one question; so are there any other issues that the FDA wanted us to consider today before we adjourn?

Okay, Marshall, yes.

DR. STANTON: Could I just ask a question on this --

CHAIRPERSON CURTIS: Sure.

DR. STANTON: --this topic?

Thank you. Marshall Stanton.

I just want -- a question to Mr. Dillard from FDA, just to clarify something in, in my mind.

Is it true, then, that a PMA supplement would not be needed as long as promotional materials are not linking data to a specific product? And it would be okay, then, to use data that's in -- that has been presented or in the literature when you're talking about the generic use of ICD therapy?

MR. DILLARD: Jim Dillard.

As broad as that question was posed, I can't probably answer it as broadly, to say that in all cases, that would be the situation. I, I think we would have to look what the particular literature was, and what it said, and how broadly that it may be able to be interpreted.

But I think, in general, part of the thought process behind what we were trying to do here today, which I think you really brought forward and were very clear about is that it will reduce, in a lot of the areas, the burden that we have in the current

situation of approving every change of an indication for use with a PMA supplement.

And so, that was a lot of the idea behind this. So I don't want to sort of subvert that by saying, you know, what I want to bring forward here is that all the small changes and indications that might come from published literature, now, walking away from this, need to come in in some way, shape, or form.

I think it's one of those that if we move in this direction, and if we have a more general intended use, a functional intended use for the products, it allows to enter into much more freely, a discussion with the manufacturer; and have the manufacturer put something forward to say, "There's a published study," for example, "we think it contains this kind of information; we think our product is supported by this particular set of data."

And it opens up the opportunities that we have for the types of regulatory submissions, either being pre-market or post-market types of opportunities, so that we now have the freedom to say, "In this case, you only need to have data on file,"

for example, "you only need to document to your file for quality system purposes why you believe the data is supportive of your particular device and you don't need a pre-market submission."

Whereas in other cases, we have other opportunities; things like a 30-day, special labeling being effected that can happen in 30 days. We've got real time review. We've got other opportunities; because what we've done is we've put forward a broad, generic intended use, which allows us more flexibility with the tools that we have available to say, "Yes, this can be a purely post-market kind of situation where you just document to the file."

Whereas now, we really don't have that many options, since we've gone so specific with the uses.

So, I, I think what it allows us to do is not have such a formalized policy, where everything has to be a pre-market submission. It allows us to be able to do what I think FDA may intended us to do, which is work interactively with the sponsor, so that we can figure out which one of those do we need to

participate in and which ones do we not need to participate in.

DR. STANTON: So, for example, would the recently published MUSTT trial be something that would not need a PMAS?

MR. DILLARD: Well, I, I would say that, that -- that has come up in a number of different forums. And would there be a need to sit down and have that discussion?

I think, at this point, we're not willing to go forward and say that we've come to the same point that you have in industry, to say, "We don't want to have that conversation, we've already decided that you don't need a PMA supplement."

I think, at this point, what we would say is, "Let's sit down and let's look at that; and let's see if it's genericizable; and if it is, we'll make a reasonable decision about whether or not it needs to be a PMA supplement or not."

But it allows us to be able to have that conversation; whereas right now, under the current situation, it doesn't. It's just an automatic PMA

supplement.

CHAIRPERSON CURTIS: So it sounds to me like what we get to is, instead of you have to have a PMA supplement all time, what you're saying is, you often may not need one, --

MR. DILLARD: Right.

CHAIRPERSON CURTIS: -- but you got to check.

MR. DILLARD: Right.

CHAIRPERSON CURTIS: Renee?

DR. HARTZ: I would just like to throw out for discussion the possibility that one word in this statement might solve some of these issues with pre-imposed marked submissions; and that would be "the defibrillator is intended to provide ventricular anti-tachycardial pacing and ventricular defibrillation for automated treatment of documented life-threatening ventricular arrhythmias."

Because that brings in the literature, and it brings in the fact that there is really, truly, an obligation on the part of the implanter to have a documented indication. I just --

CHAIRPERSON CURTIS: Yes, but, see, the problem is that there are indications now where, where patients are getting prophylactic defibrillators, where you don't necessarily have a documented arrhythmia already.

DR. HARTZ: Oh, yes, because the -- that, that literature will address that a patient with an ejection fraction of below a certain percent, with an ischemic myopathy is at risk for -- of ventricular arrhythmia. You see what I'm saying? Even --

DR. BAILEY: But that's not a --

DR. HARTZ: -- if the patient is not --

DR. BAILEY: -- documented arrhythmia, it's just a documented need.

DR. HARTZ: "Treatment of documented, life-threatening ventricular arrhythmias." That means that the patient has a potential for having.

See, I'm trying to get in somewhere that we have a word that says if the patient falls into a category that may have a life-threatening arrhythmia.

CHAIRPERSON CURTIS: It's, it's -- to me, and I think other people around the table are feeling

the same way.

If you say "documented," that means you have to have the EKG strip showing the arrhythmia.

DR. HARTZ: Well, I don't know, that's --

CHAIRPERSON CURTIS: That's what "documented" means to me.

DR. TRACY: Yes, I think that that's sort of traditionally the -- would be electrophysiologic way of looking at it, that you have documented the actual rhythm that you're treating, as opposed to want you want to add in there, some idea that it's documented to be of benefit in this particular patient population.

This statement is, is functional; it just says, "This device can recognize and treat if a life-threatening arrhythmia occurs." As opposed to making any statement about the indication, the particular indication.

So, I, I think that, to go back and add the word "documented," gets us back to where we are right now, where there are some documentation of, of benefit for a particular patient population as to

prove -- as opposed to generically saying "device sees and treats life-threatening arrhythmia."

CHAIRPERSON CURTIS: Go ahead.

Well, we're near the end, here, if we -- a couple of public comments, that's fine.

DR. DEVRIES: Dale DeVries.

I guess I would address this to the FDA. We are working under the assumption that a manufacturer can still submit for approval of an indication for a specific patient population as an indication.

MR. DILLARD: Jim Dillard.

That, that, in fact, is still true. So that if you do want to have a specific population that you think your particular type of product is of benefit for, you can still submit to us.

I think this is a little bit of a change in policy for us, where it's not of necessity --

DR. DEVRIES: Okay.

MR. DILLARD: -- now. It's now -- places a lot of the decision-making on your side, to say, geez, is it of some benefit to us to actually try to

have this added to our labeling, or can we just live with a generic use, where the physician then decides whether or not it's the appropriate patient population?

DR. DEVRIES: I just wanted to have it --

MR. DILLARD: Yes.

DR. DEVRIES: -- that it was not precluded from doing.

CHAIRPERSON CURTIS: All right.

Any other comments?

(No response)

CHAIRPERSON CURTIS: If not, I think we can adjourn.

MR. DILLARD: Thank you again; appreciate all of your input; and we'll see you next time.

(Whereupon, the foregoing matter adjourned at 11:13 a.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Circulatory System Devices Panel of the Medical Devices Advisory Committee

Before: DHHS/FDA

Date: June 20, 2000

Place: Gaithersburg, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.